Opposition of Environmental Defense and Keep Antibiotics Working to Motions for Stay of Effective Date of Withdrawal of Approval for Use of Enrofloxacin (Baytril) in Poultry (FDA Docket No. 00N-1571).

Environmental Defense, on behalf of itself and other members of the Keep Antibiotics Working coalition,[1] opposes the motions to stay the effective date of the Final Decision and Order issued by the Commissioner on July 28, 2005 pending judicial review. That Decision withdraws approval for use in poultry of enrofloxacin, a fluoroquinoline antibiotic sold under the trade name Baytril. Three such motions have been filed: one by Bayer Corp., the sole producer of the Baytril; a second by the Animal Health Institute (AHI), a trade association representing Bayer and other manufacturers of animal drugs; and a third by the American College of Poultry Veterinarians and similar organizations (hereinafter referred to jointly as ACPV). Bayer makes no substantive arguments in its petition, but instead merely joins in those raised in the ACPV petition. Bayer's Petition also states that Bayer "commits" to keep marketing Baytril for poultry use if the stay is granted (Bayer petition at 2).

Under FDA regulations, before issuing a stay the Commissioner must conclude that four distinct criteria are met: (i) the petitioner will suffer irreparable injury absent a stay; (ii) appeal is not frivolous and is sought in good faith; (iii) there are sound public policy grounds supporting the stay, and (iv) delay is not outweighed by public health considerations. As demonstrated below, *none* of these factors is met. Because we believe that public health considerations should be the starting point for this analysis – as they are under the Food Drug and Cosmetic Act – we address the final criterion first.

1. The Delay Resulting from the Stay Will Be Outweighed by Public Health or Other Public Interests

Even if ACPV, AHI, and Bayer could successfully meet the other three requirements for issuance of a stay (though as demonstrated below they cannot), the stay should nonetheless be denied in light of the significant public health consequences of fluoroquinolone resistance, together with the fact that continued use of Baytril promotes development and spread of fluoroquinolone-resistant bacteria. As explained below, consequences of resistance include not only decreased effectiveness of fluoroquinolones for treating *Campylobacter*, but also increased virulence in *Campylobacter* (and probably in other bacteria exposed to

[1] Keep Antibiotics Working (KAW) is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with a joint membership of more than nine million members. KAW seeks to reduce the growing public health threat of antibiotic resistance by curtailing improper use of antibiotics, particularly in animal agriculture. (KAW is supportive of efforts to curtail misuse of antibiotics in human medicine but focuses its work primarily in agricultural antibiotics because few other organizations do so.) Even prior to FDA's issuance of the Notice of Opportunity for Hearing in October 2000, KAW and its members have actively sought to have FDA withdraw approval for use of fluoroquinolones in poultry.

2000N-1571

CH 12

fluoroquinolones as a result of their use in poultry). Although resistance affects only those *Campylobacter*-infected patients who undergo antibiotic treatment, increased virulence affects *all* persons infected by the resistant bacteria.

The relationship between resistance and increased virulence is described in detail by FDA's parent agency, the Department of Health and Human Services, in official comments on a 2004 report by the Government Accountability Office:[2]

> Recent studies have demonstrated that antimicrobial resistance among foodborne bacteria, primarily *Salmonella* and *Campylobacter,* may cause prolonged duration of illness, and increased rates of bacteremia, hospitalization, and death. . . .
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> Several *Campylobacter* case-control studies in the United States and Denmark have demonstrated a relationship between quinolone resistance and prolonged duration of illness. GAO does mention the Smith *et al.* study in Minnesota[10], but there are several others that GAO ignores. In a 1996-1997 study in Denmark, Neimann *et al.* found that among *Campylobacter* cases treated with fluoroquinolones or other antibiotics, ***the median duration of illness was 14 days in patients infected with ciprofloxacin-resistant strains compared to 9 days in patients with susceptible isolates.***[11]
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> Nelson *et al.* conducted a multistate case-control study of sporadic *Campylobacter* cases in the United States in 1998 and 1999.[12] Among patients who did not take antidiarrheal medications, patients with ciprofloxacin-resistant infections had a longer mean duration of diarrhea than those with ciprofloxacin-susceptible infections (9 vs. 7 days, p=0.04). The difference in mean duration of diarrhea between ciprofloxacin-resistant and ciprofloxacin-susceptible infections was even more pronounced among persons who did not take antidiarrheals or antimicrobials (12 vs. 6 days, p=0.04), suggesting that resistant *Campylobacter* may be more virulent than susceptible strains. In a multivariate model controlling for antimicrobial, antidiarrheal, and antacid use, ***the mean duration of diarrhea was longer for patients with ciprofloxacin-resistant infections*** than for patients with susceptible infections (p=0.01) and the effect was independent of foreign travel.[12]
>
> A recently completed study in Denmark evaluated the relationship between resistance in *Campylobacter* and increases in both bacteremia and mortality. Among patients with culture-confirmed campylobacteriosis from 1995 to 2000, ***those with fluoroquinolone-resistant or erythromycin-resistant Campylobacter***

[2] U.S. Government Accountability Office, Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals (report no. GAO-04-490). Available at http://www.gao.gov/new.items/d04490.pdf (accessed Sept. 1, 2005) (emphases added).

infections were more likely to have a bloodstream infection or die in the 90 days following specimen collection than those with susceptible infections.[1]

ACPV's argument that public health will be unaffected during judicial review is unpersuasive. ACPV states that the Final Decision "notes that the actual incidence of infections from such resistant *Campylobacter* has decreased" since FDA approved enrofloxacin (ACPV petition at 12, without citation to the Decision). But in actuality, the Decision states just the opposite: "The proportion of *Campylobacter* infections that is resistant to fluoroquinolones has *increased significantly* since the use of enrofloxacin was approved in the United States" (Decision at 120 (emphasis added)).

Indeed, the increase has been so significant that the total number of fluoroquinolone-resistant *Campylobacter* infections rose even though the numbers of total cases has fallen in recent years. As researches from the Centers for Disease Control point out, "the incidence of ciprofloxacin-resistant *Campylobacter* infection increase[d] an estimated 46%, from 1.4 infections/100,000 persons during 1997 to 2.0 infections/100,000 persons during 2001."[3]

ACPV has offered no basis for its implicit assertion that continued use of fluoroquinolones in poultry during judicial review will not continue to promote the development and spread of fluoroquinolone-resistant *Campylobacter*. Even if fluoroquinolone-resistance rates in *Campylobacter* is currently falling, the relevant public-health question is whether they would fall *faster* if fluoroquinolone use in poultry were discontinued during the judicial review process. Despite ACPV's reference to "a few more months" (ACPV Petition at 12), final resolution could in fact take several years, particularly if Bayer and its allies continue to exploit every avenue for delay (e.g., following a decision by the D.C. Circuit, then seeking rehearing, rehearing en banc, and Supreme Court review). Indeed, in two cases discussed at length by the Commissioner, more than three years lapsed between the filing of the appeal in the Court of Appeals and issuance of a Supreme Court decision.[4]

In sum, consideration of health effects demonstrates that the Commissioner should not grant a stay pending judicial review.

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[3] JM Nelson, RV Tauxe, and FJ Angulo (2005). Reply to Cox et al. *J. Infectious Disease* 2005 (191): 1567-68.

[4] In *American Trucking*, nearly four years elapsed between filing an appeal in the U.S. Court of Appeals for the District of Columbia and the Supreme Court's issuance of its opinion. *Whitman v. Am. Trucking Assn*, 531 U.S. 457 (U.S. 2001) (affirming in part and reversing in part, 175 F.3d 1027 (D.C. Cir. 1999)). In *Donovan*, over three years elapsed between these two events. *American Textile Manufacturing Institute v. Donovan*, 452 U.S. 490 (1981) (affirming in part and vacating in part 617 F. 2d 636 (D.C. Cir., 1979)).

2. Petitioners Will Not Suffer Irreparable Harm If the Stay is Not Granted

A. Claims of Harm by American College of Poultry Veterinarians et al. Lack Merit.

ACPV argues that it will suffer irreparable harm because its "members will not be able to treat chickens and turkeys in a way that is effective..." ACPV Petition at 5-6. Even assuming for the sake of argument that there are no effective alternatives to enrofloxacin, ACPV fails to explain how this results in either an economic or a non-economic loss *to its members*. ACPV makes no claim that its members have any ownership or other direct financial interest in the flocks in question. Given that fluoroquinolones are used in, at most, only 1-2% of broiler flocks and 4% of turkey flocks annually (Decision, p. 23), it plainly cannot be said that the viability of the entire poultry industry – and thus of the profession of poultry veterinarian – depends on the availability of fluoroquinolones.

Nor does ACPV explain how its members would suffer any non-economic loss. ACPV does not claim that lack of treatment causes serious pain and suffering in the animals beyond that ordinarily experienced in commercial poultry operations, or that its members would themselves suffer greatly even if such animal suffering actually occurred, or why euthanasia of infected birds would not be an option in that event– these are, after all, birds that will shortly be sent to the slaughterhouse (chickens are slaughtered around age seven weeks,[5] and turkeys at age sixteen weeks[6]). Finally, even if ACPV members experience frustration as a result of their alleged inability to provide "effective" alternative treatments, this type of professional frustration hardly rises to the level of an irreparable harm.

ACPV next argues that "many smaller producers" could be put out of business absent a stay. Aside from the fact that these assertions are inconsistent with the fact that Baytril is used only is a very small fraction of poultry flocks as noted above, the absence of any actual poultry producers from the roster of petitioners seeking a stay undercuts the credibility of these claims. Furthermore, ACPV simply offers conclusory allegations about economic impacts, perhaps because the Commissioner found that that the economic evidence in the record was "not sufficiently reliable to be given any weight" (Decision at 108).[7]

Finally, ACPV argues that "irreparable harm" will result if a stay is not issued because chicken and turkey producers will have had only "minimal time" to find alternatives to Baytril use since the Commissioner's July 28, 2005 decision. But CVM issued the Notice of Opportunity for Hearing on the proposed withdrawal of approval in October 2000; the

[5] See http://ceinfo.unh.edu/Pubs/HGPubs/Broilers.pdf (last accessed on September 1, 2005).

[6] See http://ianrpubs.unl.edu/poultry/nf246.htm (last accessed on September 1, 2005).

[7] In striking this evidence as irrelevant as well as unreliable, the Commissioner noted that "FDA is not authorized, under the FDCA, to weigh economic . . . benefits that the drug provides against a health risk to the ultimate human consumers of food from or contaminated by treated animals" (Decision p. 120).

ALJ issued his Initial Decision upholding CVM in March 2004; and the parties filed their final papers for the Commissioner's review on July 16, 2004 (Decision at 5). If poultry producers took no steps to ready themselves to forego fluoroquinolone use during the intervening fourteen months since those papers were filed (not to mention the four preceding years), they have no one but themselves to blame.

Moreover, ACPV argues that there are no existing alternatives, dismissing the availability of sulfa drugs on the ground that their use "poses a serious risk of product residues." But such residues can be avoided by halting use of the drug the requisite period prior to slaughter, known as the withdrawal period. While the withdrawal period for sulfadimethoxine in broilers is three days longer than that for Baytril this does not mean that sulfadrugs are unavailable as an alternative to Baytril though they may be slightly less convenient from a poultry producer's standpoint.

ACPV's claims about lack of alternatives to Baytril are further undercut by the fact that that most major chicken producers have already publicly stated that they do not use these drugs in chicken produced for human consumption, including Tyson, Gold Kist, Perdue, Foster Farms, and Claxton.[8] Additionally, major chicken purchasers, including McDonald's, Wendy's, Dairy Queen, Burger King, Domino's, Hardee's, Popeye's, Subway and Bon Appetit have instructed their suppliers to stop using fluoroquinolones in chickens they purchase.[9] Indeed, McDonald's, probably the nation's largest purchaser of poultry meat, does not allow use of fluoroquinolones in chicken produced for McDonald's.[10] In written testimony submitted to FDA, McDonald's Vice-President for Worldwide Quality Assurance explained that McDonald's "believe[s] the human health risks posed by the use of fluoroquinolones in poultry are serious and supported by sounds science."[11]

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[8] See www.keepantibioticsworking.org/new/consumers_statements.cfm#prod (last accessed on September 1, 2005).

[9] See www.keepantibioticsworking.org/new/consumers_statements.cfm#prod (last accessed on September 1, 2005).

[10] See Written Direct Testimony of Kenneth M. Koziol, VP for Worldwide Quality Assurance at the McDonald's Corporation (December 9, 2002).

[11] See Written Direct Testimony of Kenneth M. Koziol, VP for Worldwide Quality Assurance at the McDonald's Corporation (December 9, 2002).

B. Claims of Harm by the Animal Health Institute Lack Merit.

The Animal Health Institute (AHI) offers the curious argument that it will be irreparably harmed absent a stay because FDA's reasoning in banning fluoroquinolones for poultry would have the "practical effect" of preventing any future approval of any antibiotic for administration via feed or water (AHI Petition at 2). This argument (flawed though it is on many grounds) may indicate why AHI urgently hopes that the D.C. Circuit will reverse the Commissioner's decision on appeal, but says nothing at all about how AHI will be harmed if fluoroquinolones cannot be used *during* the appeal. As such, AHI has failed to offer any cognizable basis for seeking a stay, and its motion should be denied on that basis alone.

C. Bayer Corporation Does Not Even Make a Claim of Irreparable Injury.

Bayer's own Petition for Stay does not even purport to claim that it will be irreparably harmed absent a stay; rather, it merely joins in the ACPV claims, but those claims do not relate at all to Bayer. In addition, Bayer "commits to keep enrofloxacin on the market for the approved use if the stay is granted" (Bayer petition at 2). As a result, Bayer's motion for stay is inadequate on its face and should be denied.

3. The Grounds On Which Review Is Sought Are So Lacking In Merit As To Be Frivolous.

Although ACPV and AHI raise various scientific and legal arguments, each of those arguments so plainly lacks merit that it qualifies as frivolous. As an initial matter, ACPV states that the Commissioner's decision is precedent-setting (ACPV Petition at 7); though this is indeed the case, the real question is whether ACPV identifies any nonfrivolous grounds on which to challenge the decision. As describe below, ACPV fails to do so.

ACPV next asserts that FDA failed to define "what 'safety' means in the contexts of a bacterium naturally present in the food chain" (ibid.). This is irrelevant even if true, as FDA had no obligation or need to do so here, where the question is whether the drug use is "not shown to be safe."

Third, ACPV cites the voluminous pleadings filed by Bayer and its allies (ACPV at 8), apparently mistaking quantity for quality. The fact that CVM filed lengthy responsive pleadings simply reflects the need to rebut Bayer's voluminous materials. Indeed, both the Administrative Law Judge (ALJ) and the Commissioner struck as irrelevant and/or unmeritorious substantial portions of Bayer's materials. Material that were stricken as unreliable included the testimony of Louis Anthony Cox Jr., who the Commissioner found unreliable because of his practice of misquoting scientific literature (Decision, p. 16-17); evidence on economic impacts (Decision, p. 108), environmental impacts (Decision, 111), availability of alternatives (Decision, p. 111), and human health benefits

(Decision, p. 112-119). In short, the fact that Bayer *et al.* filed many pages says nothing about whether they raised meritorious issues, much less that there are nonfrivolous grounds for appealing the Commissioner's decision.

Fourth, ACPV argues that there are significant legal issues raised by the Commissioner's decision, including whether the Commissioner properly interpreted the Food, Drug, and Cosmetic Act to preclude him from considering evidence of human health benefits (ACPV petition at 8). ACPV acknowledges that the Commissioner nonetheless evaluated the evidence proffered on this point and *rejected* it (ACPV Petition at 9), stating it was "unreliable as a matter of science and not probative as a matter of law" after a seven-page single-spaced discussion (Decision at 112-119). Accordingly, the Commissioner's decision would be reversed on appeal if and only if the reviewing court *both* rejected his statutory interpretation *and* his scientific evaluation. Bayer et al. have a heavy burden to bear on both grounds, because the courts normally grant deference both to an agency's construction of the statutes it administers and – to an even greater degree – to its scientific judgments. Commissioner Crawford's scientific evaluation in this matter is particularly worthy of deference, as he himself is a veterinarian who also holds a Ph.D. in pharmacology.

Last, ACPV makes passing references to Bayer's far-fetched assertions that data generated after FDA approved Baytril for use in poultry did not constitute "new" data, and that individual studies must be evaluated in isolation rather than evaluating the evidence as a whole (ACPV Petition at 9). Again, these grounds are so substantively lacking in merit as to constitute frivolous grounds for appeal, particularly in light of the Commissioner's thorough and persuasive rejection of them in the Decision.

Finally, AHI offers vague speculations that "the decision may have a ripple effect" that would chill future development of additional agricultural drugs (AHI Petition at 3). But this says nothing about whether there are substantive grounds for appeal of the Commissioner's decision (indeed, it is more akin to an element of irreparable harm, though AHI's bald assertion is far too speculative to be persuasive in this regard).

4. Sound Public Policy Does Not Support Bayer's Request for a Stay

ACPV argues that there are three public-policy considerations warranting a stay, but all three are variations on a single theme – one that plainly lacks merit. First, ACPV expresses the hope that the D.C. Circuit will reverse the Commissioner's legal interpretation under which he concluded that he was not permitted (or, if permitted was not required) to consider the alleged health benefits of fluoroquinolone use, and then concludes that such a reversal would "necessitat[e] a re-review of the matter" (ACPV Petition at 10). But even if the court does issue such a reversal, as noted above the Commissioner has *already* completed the very analysis that would be required, explaining in detail why the proffered evidence was rejected as "unreliable as a matter of science and

not probative as a matter of law" (Decision at 119). In other words, the "re-review" has already happened, though not yielding ACPV's desired result.

ACPV's second claim, about the desirability of a reading by the DC Circuit as to the statutory interpretation issue, is merely a variation of the first claim. Again, ACPV ignores the fact that *even if the Commissioner's statutory interpretation is invalidated*, his Decision will stand unless the DC Circuit takes the extraordinary step of invalidating his carefully reasoned rejection of the evidence of alleged human-health benefits.

ACPV's third argument is, yet again, that the alleged human-health benefits of enrofloxacin should be considered. And yet again, ACPV fails to present any convincing policy argument as to why the Commissioner should stay his Decision, given that he rejected the proffered evidence on those very benefits as unreliable and not probative.

Indeed, sound policy argues strongly *against* the granting of a stay. This proceeding has already lasted nearly five years, due in no small part to the voluminous filings by Bayer *et al.*, which in turn prompted detailed rebuttals from CVM. In his final Decision, the Commissioner noted that "Large portions of Bayer's exceptions [to the ALJ's initial decision] do not comply with [the regulations governing appeal to the Commissioner of an ALJ decision] . . . . Additionally, many of Bayer's exceptions are frivolous or trivial" (Decision at 5).

The Administrative Law Judge similarly complained about the sheer volume of Bayer's filings (and the responses they prompted from CVM):

> I hate to cry poor, but I'm pretty much by myself, with an occasional assistance from a law student in these cases, and I've got – does anybody have an idea how many thousands and thousands of pages you people have given me to look at?
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> No one wants to venture a guess? Three thousand proposed findings of fact? Three thousand?
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> Never in my 30-some years on the bench have I seen 3,000 proposed findings of fact, and both sides are guilty, 1,500 or more from each side. There's only four or five issues in this case. I know they're not simple issues, but that's ridiculous.
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> Six hundred pages of replies to motions to strike? A lot of repetition....[12]

These dilatory tactics used by Bayer et al. should not be rewarded by issuance of a stay at this juncture.

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[12] Transcript of Hearings before ALJ, at 625-27 (May 2, 2003), www.fda.gov/ohrms/dockets/dailys/03/May03/050903/00n-1571-tr00005.DOC (last accessed, Aug. 23, 2005).

In sum, the petitions fail to meet any, much less all, of the criteria governing issuance of a stay. The Commissioner should accordingly deny the stay.

Respectfully submitted,

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